Blood, bones and brains : peripheral biological endophenotypes and their structural cerebral correlates in psychotic disorder

CHAPTER

Ten

Valorization

The cost of schizophrenia and other psychotic disorders is high. Not only do patients pay by the disease burden they experience in daily life, their lives are cut short by more than ten years compared to the unaffected population. Increased mortality risk may only be ascribed to suicide for a small part; the better part is due to less access to health care, lifestyle factors and possible iatrogenic effects of treatment, e.g. metabolic syndrome due to second generation antipsychotic medication (Laursen et al., 2013; Saha et al., 2007; van Os and Kapur, 2009). The economic cost for society is accordingly high (Kennedy et al., 2014).

Despite these grim statistics, schizophrenia is not necessarily the debilitating and deteriorating disease it was once thought to be. Prospective studies show that outcome varies greatly a year after diagnosis. Roughly a third of patients show good outcome, another third has poor outcome, with the remaining patients at an intermediate level (van Os and Kapur, 2009). Treatment generally constitutes the prescription of antipsychotic medication combined with application of supportive interventions in the patient's psychological and social context. Generally speaking, pharmacological treatment is still a one-trick pony, i.e. dopamine receptor antagonism. With advancing insights into etiological mechanisms, new treatment strategies will develop and outcome stands to improve with personal gain for patients, as well as their families, and society as a whole.

Optimistically, these developments may also alter the perception of psychotic disorder and mental illness by the general public. Individuals with psychotic disorder or any other mental illness are not to be feared or avoided. It should be understood that they are people struggling with a medical condition no different from a patient with a physical diagnosis.

Insight in etiological mechanisms in psychotic disorder can be gained by investigating endophenotypes. The studies included in this thesis aimed to examine and differentiate between potential peripheral biological endophenotypes and patient-specific characteristics, in relation to structural cerebral measures. Although no endophenotypes were identified, the patient-specific findings described in this thesis can certainly benefit individuals with psychotic disorder.

Our work has provided new evidence for the estrogen hypothesis of schizophrenia with support for both of its aspects, i.e. estrogen deficiency due to gonadal dysfunction and estrogen-mediated neuroprotection providing a relative defense against psychotic disorder. BMD was found to be reduced in female patients and is possibly indicative of estrogen deficiency. Higher cumulative exposure to estrogen was associated with increased cerebral cortical thickness in women with psychotic disorder. The longitudinal data provided no evidence of continuous low estrogen levels (reflected by excessive loss of bone mass) in psychotic disorder.

Our studies provide a theoretical basis to explain the efficacy of augmentation of estrogen and selective estrogen receptor modulators (SERMs) to antipsychotic treatment. To date, clinical trials were performed on the premises of epidemiological sex differences while studies with a primary biological perspective were lacking.

Reduced BMD due to secondary disease factors (such as lifestyle and iatrogenic effects of PRL-raising AP) deserves to be recognized as an important issue. Awareness of increased prevalence of osteoporosis and fracture risk is warranted in the comprehensive treatment of all health concerns in patients with psychotic disorder.

Serum S100B has been heralded as a promising candidate marker in psychotic disorder. However, in our studies, serum S100B was not elevated in individuals with (increased risk of) psychotic disorder in two large independent samples. Nor did we find proof of the validity of S100B as a proxy marker for grey and white matter status in healthy individuals or patients with psychotic disorder. From the literature, it appears that S100B is possibly too sensitive and too indiscriminate to be useful. S100B elevation is perhaps merely indicative of mental activity and/or stress as it is has been shown in physicians on duty, activity which may indeed be stressful but not quite pathological (Gazzolo et al., 2010).

In general, it should be remembered that negative findings make important scientific contributions and are crucial in marking directions for future research. This will ultimately benefit patients, the file drawer effect will not.

The concept of linking peripheral endophenotypes to cerebral structure (or function) is a potentially useful tool for future research. It may be applicable in investigating therapeutic efficacy and identifying regions of interest in the brain in experimental treatment studies, by acquiring neuroimaging data pre- and post-intervention.

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